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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,777	07/24/2001	Jeffrey Browning	A070US	3867

22852 7590 03/11/2003

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EXAMINER

HADDAD, MAHER M

ART UNIT PAPER NUMBER

1644

DATE MAILED: 03/11/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/911,777

Applicant(s)

BROWNING ET AL.

Examiner

Maher M. Haddad

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 December 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-50 is/are pending in the application.
- 4a) Of the above claim(s) 1-9, 14, 15 and 17-50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-13 and 16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6. 6) ☐ Other: _____

Art Unit: 1644

DETAILED ACTION

1. Claims 1-50 are pending.
2. A clear and obvious typographical error occurred in the restriction wherein claims 14 and 15 which reads on anti-BAFF ligand molecule of Group V were improperly included in Group VII which are drawn to an antibody specific for BAFF ligand or an active fragment thereof. Therefore claims 14 and 15 are drawn to nonelected inventions.
3. Applicant's election with traverse of Group VII, claims 10-16, (now claims 10-13 and 16) drawn to methods of inhibiting B-cell growth, inhibiting immunoglobulin production, co-inhibiting B-cell growth and immunoglobulin production and inhibiting dendritic cell-induced B-cell growth and maturation in an animal comprising the step of administering an antibody specific for BAFF ligand or an active fragment thereof filed on 12/26/02, is acknowledged.

Applicant's traversal is on the grounds that the restriction several Groups share the same classification. Further, Applicant argues that the Examiner does not explain what structural differences in the "products" or "steps" would necessitate a field of search where no pertinent art to the other subject exists. Applicant argues that the present restriction requirement is excessive and cost prohibitive to the Applicant. This is not found persuasive because different products such as the specific BAFF ligand, the anti-T antibody the CD40 ligand, anti-CD40, anti-BAFF ligand molecules, the recombinant, inoperative BAFF ligand molecules, the antibody specific for BAFF ligand and the antibody specific for the BAFF ligand receptors are recognized divergent subject matter. In addition, the methods of stimulating B-cell growth and the methods of inhibiting B-cell growth are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct *agonists* or *antagonists* to accomplish these mutually exclusive endpoints. While certain Groups share the same classification, a different field of search would be required based upon the structurally distinct products recited and the various methods of use comprising distinct method steps. Therefore, these methods are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 1-9, 14-15, 17-50 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.
5. Claims 10-13 and 16 are under examination as they read on methods of inhibiting B-cell growth, inhibiting immunoglobulin production, co-inhibiting B-cell growth and immunoglobulin production and inhibiting dendritic cell-induced B-cell growth and maturation in an animal comprising the step of administering an antibody specific for BAFF ligand or an active fragment thereof.

Art Unit: 1644

6. There is a discrepancy between the Declaration and the Specification on page 1, line 5, regarding the filing date of U.S.S.N 60/143,228. The Declaration indicates that U.S.S.N 60/143,228 was filed July 9, 1999, while the specification discloses that U.S.S.N 60/143,228 was filed July 9, 2001. Examiner notes that U.S.S.N 60/143,228 was filed July 9, 1999. Correction is required.

7. The disclosure is objected to because of the following informalities: page 8, lines 11-15, discloses that in Figure 2B, the polyclonal anti-BAFF was used however, Figure 2B depicts the use of anti-MARCH antibody. Page 9, lines 28-30, disclose the use of BAFF ligand, however, Figure 6, depicts the use of Kay Ligand (kayl). Further, page 37, lines 23-24, discloses the use of anti-CD11c for dendritic cells. Examiner notes that anti-CD1c antibody is used for dendritic cells. Appropriate correction is required.

8. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Page 28, line 3 has described three motifs in BAFF, APRIL and Tweak wherein each must have a sequence identifier. Correction is required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 10-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a method of inhibiting B-cell growth, inhibiting immunoglobulin production, co-inhibiting B-cell growth and immunoglobulin production, or inhibiting dendritic cell-induced B-cell growth and maturation comprising administering a composition of any antibody specific for any BAFF ligand, or any active fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to make and use antibodies for any BAFF ligand or any active fragment thereof. Furthermore, the specification fails to provide empirical data to show that method would work in vivo. Finally, the specification fails to show the effect of anti-BAFF antibody on B-cell isotypes.

Art Unit: 1644

Beside SEQ ID NO: 1 and 2, the present specification fails to provide sufficient disclosure of any BAFF ligand or amino acid fragments that maintain the structural and functional properties of the BAFF activity set forth in SEQ ID NO:1 and 2, wherein the fragment is active. The specification does not provide sufficient guidance as to which of the amino acids may be changed while BAFF functional activity is retained. Dogan et al (J. Biol. Chem. 270:14047-14055, 1995) disclose that a single amino acid can determine the ligand specificity of a selectin and the unpredictable nature of amino acid alterations in adhesion/binding activity (see entire document, including the discussion). Further, Colman *et al* in Research in Immunology (145(1):33-36, 1994) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Further, the current state of the art in antibody therapeutics and the predictability of treatment efficacy is complicated by the potential for antibody interactions with irrelevant or completing epitopes, Fc region engagement, reduced half life of antibody fragments, and immune response to the therapeutic antibodies (see Ward et al, pages 167-171, 1994 "consideration related to use of blocking antibodies").

The specification does not adequately teach how to effectively make and use any BAFF ligand (e.g. human BAFF, rat BAFF or the fruit fly BAFF) or any active fragment thereof, and in turn, an antibody against any BAFF ligand or any active fragment thereof to inhibit B-cell growth and immunoglobulin production by administering said antibodies encompassed by the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the claimed antibodies encompassed by the claims.

The specification on page 35, line 14-15 discloses that the overexpression of BAFF is affecting the proliferation of mature B cells in the periphery but not progenitor B cells in the bone marrow, then a method of inhibiting *pro* B-cell growth using anti-BAFF antibody is unpredictable because BAFF stimulates B cells when the cells are coactivated via their antigen receptors. Further, the specification does not adequately teach the effect of BAFF ligand on B-cell isotype. The specification on page 36, lines 1-6, teaches the increased level of total Ig in the blood of BAFF Tg mice. Therefore, it is unclear that the skilled artisan could inhibit all B-cell immunoglobulin production of all isotypes using anti-BAFF antibody.

At issue is whether or not the claimed method would function in "inhibiting B-cell growth, inhibiting immunoglobulin production, co-inhibiting B-cell growth and immunoglobulin production, inhibiting dendritic cell-induced B-cell growth and maturation". The nature of the invention is such that it would require the administration of anti-BAFF antibody that would inhibit B cell growth and immunoglobulin production. The specification (pages 33-38) discloses BAFF transgenic mice with elevated B cell numbers, expanded B cell compartments, high levels of total immunoglobulin, enlarged B cell follicles, numerous germinal centers, reduced dendritic cell numbers and increased plasma cell numbers in both spleen and MLN. The exemplification is drawn to stimulate B cell growth and immunoglobulin production using full length murine BAFF in BAFF Tg mice. The specification does not provide empirical data to show the efficacy of anti-BAFF antibody on the B-cell proliferation and survival, wherein the anti-BAFF antibody would function as inhibitor of B-cell growth and immunoglobulin production. It is not clear that

Art Unit: 1644

the skilled artisan could predict the efficacy of the anti-BAFF antibody, encompassed by the claims.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claims 10-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of a method of inhibiting B-cell growth, inhibiting immunoglobulin production, co-inhibiting B-cell growth and immunoglobulin production, or inhibiting dendritic cell-induced B-cell growth and maturation comprising administering a composition of any antibody specific for any BAFF ligand, or any active fragment thereof.

Applicant has disclosed only amino acid of SEQ ID NO: 1 and 2; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written

Art Unit: 1644

description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 10-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of copending Application No. 10/214,065. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to the same or nearly the same method of inhibiting mature B-cell growth, inhibiting immunoglobulin production, co-inhibiting B-cell growth and immunoglobulin production, inhibiting dendritic cell-induced B-cell growth and maturation in an animal comprising administering an antibody specific for BAFF ligand or an fragment thereof. Specifically, since APBF is an APRIL subunit linked to BAFF subunit, then an antibody specific for APBF or an active fragment thereof, would recognize BAFF ligand of the instant claims. Furthermore, since APRIL and BAFF cytokines share the same cognate receptors (i.e. TACI and BCMA) and BCMA and TACI bind APRIL and BAFF with relatively high affinity, therefore an antibody against APRIL, BAFF or both would inherently accomplish the same method (see Ware CF. J Exp Med. 192(11):F35-8, 2000).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Art Unit: 1644

13. Claim 16 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of copending Application No. 10/214,065 in view of Harlow *et al* (1989).

The '065 application has been discussed, *supra*.

The claimed invention differs from the reference teaching only by the recitation of monoclonal antibody in claim 16.

Harlow *et al* teach a method of producing monoclonal antibodies comprising immunizing an animal (i.e. a mouse) with a protein or portion thereof (i.e. fragments), harvesting spleen cells from said animal, fusing said spleen cells with myeloma cell line, and culturing said fused cells (i.e hybridoma) under conditions that allow production of said antibody. Harlow *et al* further teach that the monoclonal antibodies stems from their specificity, homogeneity and ability to be produced in unlimited quantities (see pages 141-157 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody using the method taught by Harlow with the APBA ligand taught by the '065 application.

One ordinary skill in the art at the time the invention was made would have been motivated to do so because the monoclonal antibodies produced exhibit a high degree of specificity and great affinity as taught by Harlow.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

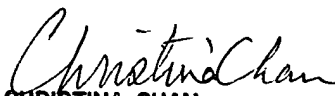
14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Art Unit: 1644

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
March 10, 2003


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